IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

10X GENOMICS, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiffs, v. PARSE BIOSCIENCES, INC., Defendant.	CIVIL ACTION NO. 22-1117

OPINION

Slomsky, J. **May 2, 2024**

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I. INTRODUCTION

On August 24, 2022, Plaintiff 10x Genomics, Inc. ("Plaintiff" or "10x") along with the Board of Trustees of the Leland Stanford Junior University ("Stanford University") as a nominal defendant[1] filed a Complaint alleging patent infringement by Defendant Parse Biosciences, Inc. ("Defendant" or "Parse"). (Doc. No. 1.) Six patents covering genomic technologies are alleged to have been infringed: 1) United States Patent No. 10,150,995 ("the '995 patent"); 2) United States Patent No. 10,619,207 ("the '207 patent"); 3) United States Patent No. 10,738,357 ("the '357 patent"); 4) United States Patent No. 10,155,981 ("the '981 patent"); 5) United States Patent No. 10,697,013 ("the '013 patent"); and 6) United States Patent No. 10,240,197 ("the '197 patent") (collectively, "the Asserted Patents").

Here, the parties seek construction of several terms of the patents-in-suit pursuant to Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996). On December 7, 2023, the parties filed a Joint Claim Construction brief that outlined the disputed claim terms and the parties' proposed constructions. (Doc. Nos. 104, 105.) On March 1, 2024, the Court held a Markman hearing on the disputed terms. The five (5) disputed terms are now ripe for construction.

II. FACTUAL BACKGROUND

In the Complaint, Plaintiffs allege that Defendant infringed the six (6) Asserted Patents, which can be grouped into two families. (Doc. No. 12 at 1.) Each group contains three (3) patents.

[1] On October 7, 2022, Stanford University was realigned as Plaintiff. (Doc. No. 9.)

(Id.) The first one includes three patents identified as the "Giresi" patents.[2] The Giresi patents include: 1) United States Patent No. 10,150,995 ("the '995 patent"); 2) United States Patent No. 10,619,207 ("the '207 patent"); and 3) United States Patent No. 10,738,357 ("the '357 patent"). (Id.) The second group includes three patents identified as the "Brenner" patents.[3] The Brenner patents include: 1) United States Patent No. 10,155,981 ("the '981 patent"); 2) United States Patent No. 10,697,013 ("the '013 patent"); and 3) United States Patent No. 10,240,197 ("the '197 patent"). (Id.)

Generally, the Asserted Patents are directed to compositions and laboratory methods used to uncover genetic information that can then be used to better understand the genetic underpinnings of human life and disease. See '981 Patent, Claim 1 ("A method of analyzing nucleic acids from a plurality of single cells . . ."); '013 Patent, Claim 1 ("A method for multiplexed analysis of nucleic acids from single cells . . ."); '197 Patent, Claim 1 ("A method of counting nucleic acids in a sample . . ."); '995 Patent, Claim 1 ("A method for analyzing a biologic sample . . ."); '207 Patent, Claim 1 ("A method for generating a sequencing library from a plurality of cells . . ."); '357 Patent, Claim 1 ("A composition comprising: a permeabilized cell nucleus[4] comprising . . .

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[2] Dr. Paul Giresi is listed as an inventor of these three patents. Also listed as an inventor is Dr. Jason Buenrostro. Defendant names the three patents discussed in this section as the "Buenrostro patents," but Plaintiffs call the same group of patents the "Giresi patents." (See Doc. No. 12 at 2; Doc. No. 14 at 1.) Plaintiffs also refers to the three patents as the "ATAC-Seq patents." (Doc. No. 33 at 18.) The Court will refer to this group of patents as the "Giresi patents" or the "Buenrostro/Giresi patents."

[3] Dr. Sydney Brenner is listed as an inventor of this group of three patents.

[4] Permeabilization is the act or process of making something, such as a cell nucleus, permeable—often through use of surfactants so the cell's contents are accessible. https://www.frontiersin.org/articles/10.3389/fchem.2019.00588/full. Surfactants are substances that decrease the surface tension of a cell so its contents become accessible.

an insertional enzyme complex . . ."). The science relevant to each group of patents will be discussed below.

A. Scientific Background

A basic overview of the relevant scientific principles is necessary to understand the patent terms at issue in this case. To begin, every cell in the human body contains chromosomes that encode genetic information. The genetic information encoded in chromosomes is comprised of deoxyribonucleic acids, or "DNA." (See '995 Patent at 8:63–9:14, 13:29–35.) DNA is a type of molecule known as a "nucleic acid" that can store genetic information. See Defs. Slide 10. Nucleic acids such as DNA are made up of chains of smaller building blocks called nucleotides. https://www.genome.gov/about-genomics/fact-sheets/Deoxyribonucleic-Acid-Fact-Sheet. A chain of nucleic acid also is referred to as a polynucleotide.[5] Each nucleotide in a polynucleotide contains one of four nitrogen bases (also known as nucleobases): 1) adenine (A); 2) thymine (T); 3) guanine (G); and 4) cytosine (C).[6] (See Defs. Slide 10.) Another type of polynucleotides is oligonucleotides, which, put simply, are small polynucleotides.[7] Stedman's Medical Dictionary 980 (24th ed. 1982).

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[5] All DNA strands are polynucleotides, but not all polynucleotides are DNA. Polynucleotides can also be RNA or other molecules. (See Defs. Slide 10.)

[6] In general, a polynucleotide is identified based on a sequence of the nucleobases. For example, the first letter of each base would create a sequence in a specific order. "A" would stand for adenine, "T" for thymine, "G" for guanine and "C" for cytosine. A sequence might look like the following: AATTGCCAAT etc. Given the number of polynucleotides in DNA, the number of different sequences is vast.

[7] Oligonucleotides are described as "small" polynucleotides because they contain less chains of nucleotides than other polynucleotides. See Pieczenik v. Dyax Corp., 76 Fed. Appx 293, 296-97 (Fed. Cir. 2003).

In this case, the Asserted Patents are focused on compositions and methods to differentiate between polynucleotides (such as DNA) within a large population of cells (the Brenner patents) (see Doc. No. 33 at 17; see e.g., '981 Patent at 6:33–7:22, 15:36–50) and to determine epigenetic[8] features in cells (the Giresi patents), (see Doc. No. 33 at 17; see, e.g., '995 Patent at 21:16–40).

i. The Brenner Patents

The Brenner patents refer to a group of three patents that Plaintiffs assert were infringed by Defendant: 1) the '981 patent; 2) the '013 patent; and 3) the '197 patent. The Brenner patents cover "methods for analyzing nucleic acids from single cells" through "tagging." (See '981 patent, '013 patent, '197 patent.) "Tags," which are also referred to as "molecular tags," also would have a sequence of nucleobases. Tags can then be used to identify a polynucleotide.[9] The method in the Brenner patents allows scientists to apply two "tags" to one polynucleotide.[10] One tag would indicate the "source"[11] or, for example, the specific cell the polynucleotide is from, and the other

[8] Epigenetics is the study of "modifications to a chromosome that impact what genes are transcribed to mRNA (which can then be expressed as proteins) without changing the chromosome's DNA sequence." (Doc. No. 104 at 9.)

[9] For example, a tag could have the sequence "ATTG," which means it is comprised of the nitrogen bases adenine, thymine, thymine and guanine.

[10] The methods for applying "tags" will be discussed in Section (IV)(A), infra.

[11] According to the '981 patent's specification, a polynucleotide's "source" could be the cell, tissue, or individual that the polynucleotide was isolated from. (See '981 patent at 6:40-44.) The '981 patent's specification states:

> For example, a nucleic acid sample may be a pool of polynucleotides derived from different sources, e.g., polynucleotides derived from different individuals, different tissues or cells, or polynucleotides isolated at different time points.

(Id.)

tag would identify the polynucleotide itself. (Pl. Slide 7.) The inventors refer to both a single tag and a combination of tags attached to a polynucleotide as a "MID."[12] (See Doc. No. 104 at 16.)

Using such methods, it is possible to differentiate between vast numbers of otherwise indistinguishable polynucleotides in a sample in order to analyze it and to count the number of different polynucleotides in each cell. (Id.)

ii. The Giresi Patents

As noted above, the Giresi patents refer to three of the Asserted Patents that Plaintiffs allege were infringed by Defendant. This group of patents includes: 1) the '995 patent; 2) the '207 patent; and 3) the '357 patent. The Giresi patents largely improve on conventional methods used to analyze open chromatin regions of DNA. (See, e.g., Doc. No. 1 ¶¶ 17, 40.) Open chromatin contains regions of nucleosomes that allow access to DNA. By contrast, closed chromatin contains regions of nucleosomes where the DNA is wrapped tightly around histones[13] and is not accessible for analysis using a MID. ('995 patent at 1:26-31, 12:54-60, 17:15-17.) Thus, scientists are interested in methods to identify and use open chromatin, rather than closed chromatin.

The Giresi patents seek to "solve[] problems associated with determining what areas of the genome are available for transcription and translation into proteins—namely regions of open chromatin." (Doc. No. 33 at 18; Tr. at 104:14–105:6.) Prior methods of analyzing areas of open chromatin required a 44-step process that few people could reproduce, a large sample size and extensive time to complete. (Doc. No. 33 at 18; Tr. at 103:12–104:13.) The inventors of the Giresi

[12] The parties agree to the construction of "multiplex identifier (MID) sequence" as "a tag or combination of tags associated with a polynucleotide whose identity (e.g., the tag DNA sequence) can be used to differentiate polynucleotides in a sample." (Doc. No. 104 at 16.)

[13] Histones are a basic form of protein found in cells.

patents determined that an engineered insertional enzyme, known as a "transposase," could be introduced into a cell nucleus and used to tagment[14] (i.e., cleaved and tagged in the same reaction) only the areas of open chromatin. (See Doc. No. 33 at 18; Tr. at 107:11–108:1; Tr. at 103:12–104:13.) This had never been done before and reduced the 44-step process to a two-step process. (Id.)

In the Giresi patents, the inventors introduced an engineered enzyme referred to as "Tn5 transposase" that can be inserted into cell nuclei to perform tagmentation inside the cell nucleus, that is, to tag a polynucleotide. Tr. at 106:25–107:3; 106:8–107:20. Previously, tagmentation could only be performed on DNA that had already been removed from the nucleus and stripped from its chromatin complex. Tr. at 76:5–20 & Parse Slide 53. The claims in two of the Giresi patents, the '995 and the '207 patents, are directed to new applications of the insertional enzyme complex, transposase, by inserting it into a cell nucleus to tagment DNA found in open chromatin to create tagged DNA fragments. (Doc. No. 33 at 20.) The claims in the third patent, the '357 Patent, are directed towards a composition consisting of a man-made insertional enzyme complex (the transposase) and tagged nucleic acid fragments derived from regions of open chromatin located inside the nucleus of a cell. (Doc. No. 33 at 22; '357 Patent, Claim 16.)

III. STANDARD OF REVIEW

The first step in a patent infringement analysis is to define the meaning and scope of the claims of the patent. Markman, 52 F.3d at 976. Claim construction, which serves this purpose, is a matter of law exclusively for the court. Id. at 979. "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to

[14] "Tagmentation" is a prior art process that cleaves and tags in the same reaction "using an insertional enzyme such as Tn5 or MuA that cleaves the genomic DNA in open regions in the chromatin and adds adaptors to both ends of the fragments." (Doc. No. 104 at 66.)

appropriate sources 'in light of the statutes and policies that inform patent law.'" SoftView LLC v. Apple Inc., No. 10-cv-389, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting Phillips v. AWH Corp., 415 F.3d 1303, 1324 (Fed. Cir. 2005)).

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." Phillips, 415 F.3d at 1312 (internal quotation marks omitted). The focus of a court's analysis must therefore begin and remain on the language of the claims, "for it is that language that the patentee chose to use to 'particularly point[ ] out and distinctly claim[ ] the subject matter which the patentee regards as his invention.'" Interactive Gift Express, Inc. v. Compuserve, Inc., 256 F.3d 1323, 1331 (Fed. Cir. 2001) (quoting 35 U.S.C. § 112, 5 ¶ 2). "Claim terms are generally accorded their ordinary meaning—that is, their meaning to a skilled artisan at the time of invention" i.e., as of the effective filing date of the patent application. Intel Corporation v. Qualcomm Inc., 21 F.4th 784, 791 (Fed. Cir. 2021) (citing Phillips, 415 F.3d at 1312-13).

Generally, a person of ordinary skill in the art ("POSITA") would not understand the ordinary and customary meaning of a claim term in isolation. Phillips, 415 F.3d at 1313. As such, the ordinary meaning may be derived from "the sources available to such artisans, including 'the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.'" Intel, 21 F.4th at 791 (quoting Phillips, 415 F.3d at 1313-14).

The "most significant source" of authority is "the intrinsic evidence of record, i.e., the patent itself, including the claims, the patent specification and, if in evidence, the prosecution history." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996); see also Phillips, 415 F.3d at 1313 (holding that a person of ordinary skill in the art is deemed to have read

the claim terms "in the context of the entire patent", including the specification). The specification is "that part of a patent application which precedes the claim and in which the inventor specifies, describes, and discloses the invention in detail." McCarthy's Desk Encyclopedia of Intellectual Property 408 (2d ed. 1995). It "is the single best guide to the meaning of a disputed term" and is usually dispositive as to the meaning of words. Vitronics, 90 F.3d at 1582 ("In most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic evidence" (citations omitted)). Although it is improper to import limitations from the specification into the claims, "one may look to the written description to define a term already in a claim limitation, for a claim must be read in view of the specification of which it is a part." Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1248 (Fed. Cir. 1998). On occasion, "the specification may reveal a special definition given to a claim term . . . that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." Phillips, 415 F.3d at 1316. The specification may also "reveal an intentional disclaimer, or disavowal, of claim scope by the inventor . . . [, which] is regarded as dispositive." Id. "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." Renishaw, 158 F.3d at 1250.

The court "should also consider the patent's prosecution history, if it is in evidence." Markman, 52 F.3d at 980. This consists of "the complete record of proceedings before the Patent Office and includes the prior art cited during examination." Phillips, 415 F.3d at 1317. "Like the specification, the prosecution history provides evidence of how the [Patent and Trademark Office] and the inventor understood the patent." Id. at 1317. The prosecution history may "'demonstrat[e] how the inventor understood the invention and whether the inventor limited the invention in the

course of prosecution . . . " SpeedTrack, Inc. v. Amazon.com, 998 F.3d 1373, 1377 (Fed. Cir. 2021) (quoting Phillips, 415 F.3d at 1317). Nonetheless, it is the least probative form of intrinsic evidence because it "represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation." Id.

If ambiguity still exists after considering all the intrinsic evidence, the court may rely on extrinsic evidence, which is "all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." Markman, 52 F.3d at 980. "[D]ictionaries, and especially technical dictionaries, . . . have been properly recognized as among the many tools that can assist the court in determining the meaning of particular terminology." Phillips, 415 F.3d at 1318. Additionally, expert testimony can provide background on the technology at issue, explain how it works, speak to what a person of ordinary skill in the art would understand, and establish that a particular term has a particular meaning in the pertinent field. Id. Extrinsic evidence, however, is "generally of less significance than the intrinsic record." Wi-Lan, Inc. v. Apple, Inc., 811 F.3d 455, 462 (Fed. Cir. 2016) (citing Phillips, 415 F.3d at 1317).

Ultimately, during claim construction, "[t]he sequence of steps used by the judge in consulting various sources is not important; what matters is for the court to attach the appropriate weight to be assigned to those sources in light of the statutes and policies that inform patent law." Phillips, 415 F.3d at 303.

IV. ANALYSIS

The parties agree on the construction of eight (8) terms. (See Doc. No. 104 at 16-17.) In dispute are five (5) terms, four (4) from the Brenner patents and one (1) from the Giresi/Buenrostro Patents. The four (4) from the Brenner patents are: (1) "combinational tagging"; (2) "wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence"; (3) "random sequences"; and (4) "digital count". The one disputed claim from the

Giresi/Buenrostro patents is (5) "adapter sequence." The Court will address each of the disputed terms in turn.

A. "combinational tagging"

Claim Term	Plaintiffs 10x and Stanford University's Proposal	Defendant Parse's Proposal
"combinational tagging"	Plain and ordinary meaning, which is "using a combination of tags, which may be added in different steps and by different methods"	"approach in which one MID is attached by ligation and a second MID is attached by primer extension"

The first disputed claim term is "combinational tagging" which appears in Claim 1 of the '013 Brenner patent. Claim 1 of the '013 Brenner patent claims:

> 1. A method for multiplexed analysis of nucleic acids from single cells, the method comprising:
>
> (a) providing a sample comprising a plurality of cells, wherein a single cell of the plurality of cells comprises a plurality of sample polynucleotides;
>
> (b) performing combinational tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:
>
> (A) providing an extension product by primer extension using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and
>
> (B) ligating a second oligonucleotide tag to said extension product, and. . .

('013 patent, cl. 1 (emphasis added).)

Plaintiffs 10x and Stanford University's proposed construction of "combinational tagging" is offered as the "[p]lain and ordinary meaning, which is 'using a combination of tags, which may be added in different steps and by different methods.'" (Doc No. 104 at 17.) Defendant Parse submits a narrower construction that limits "combinational tagging" to the "approach in which one

MID is attached by ligation and a second MID is attached by primer extension," because it reflects the language of the Patent itself.[15] (Id.) In sum, the question before the Court is whether "combination tagging" should be given its meaning as presented by Plaintiffs, or if it should be construed more narrowly to reflect the language of the '013 Patent. Here, the Court will adopt Defendant's proposed construction because it aligns with the intrinsic evidence of the '013 Patent.

To begin the claim construction analysis, the Court will turn first to the claim language itself because "[t]he claim construction inquiry . . . begins and ends in all cases with the actual words of the claim." Homeland Housewares, LLC v. Whirlpool Corp., 865 F.3d 1372, 1375 (Fed. Cir. 2017) (quoting Renishaw, 158 F.3d at 1248). In turning to the claim language, "[c]laim terms are generally accorded their ordinary meaning—that is, their meaning to a skilled artisan at the time of the invention." Intel Corp. v. Qualcomm Inc., 21 F.4th 784, 791 (Fed. Cir. 2021) (citing Phillips v. AWH Corp., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc)). In Intel, the Federal Circuit stated that to ascertain a claim term's meaning to a skilled artisan at the time of invention, courts:

> consult the sources available to such artisans, including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." [Phillips, 415 F.3d] at 1314 (quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "Importantly," skilled artisans are "deemed to read the claim term . . . in the context of the entire patent." Id. at 1313. Even when seeking the "broadest reasonable construction in light of the specification," 37 C.F.R. § 42.100(b) (2017), we still give words "their plain meaning" unless "inconsistent with the specification and prosecution history." Arista Networks, Inc. v. Cisco Sys., Inc., 908 F.3d 792, 796–98 (Fed. Cir. 2018) (rejecting construction as "overly broad, even under the broadest reasonable interpretation standard"). "Above all, the broadest reasonable interpretation must be reasonable in light of the claims and specification." PPC

[15] "Ligation" is the process of joining together chemical chains. "Primer extension" is the technique whereby the ends of RNA or DNA can be mapped, that is, they can be sequenced and properly identified.

> Broadband, Inc. v. Corning Optical Commc'ns RF, LLC, 815 F.3d 747, 755 (Fed. Cir. 2016).

Id. at 791. Specifically, the court's "inquiry is not limited to an analysis of the phrase in isolation" as "a term can be defined only in a way that comports with the instrument as a whole." Id. at 792 (citing Hockerson-Halberstadt, Inc. v. Converse Inc., 183 F.3d 1369, 1374 (Fed. Cir. 1999); Markman, 517 U.S. at 389). When looking at the instrument as a whole, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." Phillips, 415 F.3d at 1314. The Federal Circuit has clarified that a court can "rely[] heavily on the claim language to construe the claim term," especially when "the claim itself contains a precise definition of the term." TIP Systems, LLC v. Phillips & Books/Gladwin, Inc., 529 F.3d 1364, 1369 (Fed. Cir. 2008).

Defendant's proposed construction reflects the meaning a skilled artisan would derive from the language of the claim itself. Specifically, Defendant's proposed construction aligns with the intrinsic evidence of the Patent because the language of Claim 1 defines the term "combinational tagging."

> As stated previously, Claim 1 states that the '013 patent:
>
> perform[s] combinational tagging . . . by . . . (A) providing an extension product by primer extension . . . and (B) ligating a second oligonucleotide tag . . .

('013 Patent, cl. 1 (emphasis added).) This language supports Defendant's proposed claim construction because the presence of the word "by" shows that (A) and (B) are describing "combinational tagging."

While Plaintiffs contend that Claim 1 merely describes an "example" of how "combinational tagging" can be performed, they point to no words or phrases in Claim 1 that indicate that (A) and (B) are only examples. Rather, they rely on Apple Inc. v. Wi-LAN Inc., in

arguing that if this Court found that "combinational tagging" is defined by (A) and (B) in Claim 1, this claim construction would improperly narrow "combinational tagging" because there were "no 'words or expressions of manifest exclusion or restriction." 25 F.4th 960, 968 (Fed. Cir. 2022) (citing Hill-Rom Servs., Inc. v. Stryker Corp., 755 F.3d 1367, 1371 (Fed. Cir. 2014)). Defendant's reliance on Apple, however, is misplaced.

In Apple, the Federal Circuit affirmed the district court's refusal to construe "subscriber unit" as the term "CPE"[16] because "[t]he terms are never used to describe the same facet of a device or embodiment, nor are they used to refer to the same element of a figure." Id. at 967. However, Apple is not on point here for two reasons. First, Apple involves embodiments, which have less weight in claim construction than claim terms.[17] Second, in Apple, the two terms were only used in the same sentence once, where the word "or" separated the terms. Here, "combinational tagging" and Defendant's proposed construction are in the same claim and are separated by the word "by" which indicates that the phrases are related.

Furthermore, the Federal Circuit's decision in TIP is more on point to the patent-at-bar than the one in Apple. See TIP, 529 F.3d 1364 (Fed. Cir. 2008). In TIP, the Federal Circuit affirmed the district court's construction of the term "handset" as "a handle with an earpiece at one end and a mouthpiece at the opposite end" because the claim gave an "express definition" of the term

[16] "CPE" is an acronym for "fixed or portable customer premises equipment." Id. at 965.

[17] An embodiment is the physical form of the invention. "Preferred embodiments" can be added to the specification portion of a patent to describe a potential physical manifestation of the patent. While embodiments can be considered by a court during claim construction, courts "do not read limitations from the embodiments in the specification into the claims." Hill-Rom Services, Inc. v. Stryker Corp., 755 F.3d 1367, 1371 (Fed. Cir. 2014). Thus, Apple is not on point here because that case involved embodiments used as an "example." The court in Apple rejected equating the term with an example. Here, the claim language coincides with the term in dispute.

"handset" in the claim. Id. at 1370. There, the claim language the Federal Circuit found to be a "express definition" was:

> a telephone handset being a handle with an earpiece at one end and a mouthpiece at the opposite end.

Id. at 1367 (citing '169 patent, cl. 1) (emphasis added). The Federal Circuit found "no error by the district court in relying heavily on the claim language to construe the claim term." TIP, 529 F.3d 1364 at 1369 (emphasis added).

Here, as in TIP, where "being" connected the disputed term and the definition, in this case, "by" connects the phrase "combinational tagging" and the language used in (A) and (B). Thus, (A) and (B) are the "express definition" of "combinational tagging." And (A) and (B) describe how one MID is attached by ligation and a second MID is attached by primer extension.

Further, the '013 patent specification also supports Defendant's proposed construction. The '013 patent's specification states:

> Further, MIDs can be generated in a variety of different ways, e.g., by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension.

('013 patent, 7:25-27) (emphasis added). Similar to the use of the word "by" in Claim 1, the words "in which" also indicate that the preceding language will describe how "combinational tagging" is performed, and, once again, the Patent describes the process of attaching one MID by ligation and a second MID by primer extension.[18]

[18] Plaintiffs argue that because "e.g." is used, it is "not meant to indicate that the only way MIDs can be generated using a 'combinational tagging approach' is through a combination of ligation and primer extension." (Doc. No. 104 at 19.) This argument fails because it misstates the text. "E.g." means "for example". e.g., Merriam-Webster Dictionary.com, https://www.merriam-webster.com/dictionary/e.g. (last visited April 30, 2024). Thus, in replacing e.g. with "for example" the text reads:

Finally, the intrinsic evidence of the '013 patent's prosecution history also supports Defendant's proposed construction. A court "should also consider the patent's prosecution history, if it is in evidence." Markman, 52 F.3d at 980. The prosecution history may "'demonstrat[e] how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution ...." SpeedTrack, Inc. v. Amazon.com, 998 F.3d 1373, 1377 (Fed. Cir. 2021) (quoting Phillips, 415 F.3d at 1317). Specifically, as described in Trans Video Electronics, Ltd. v. Sony Electronics Inc., No. C 09-3304 MHP, 2011 WL 1884358, at *3 (N.D. Cal. May 18, 2011):

> "Arguments and amendments made during the prosecution of a patent application and other aspects of the prosecution history, . . . must be examined to determine the meaning of terms in the claims." Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995), cert. denied, 516 U.S. 987, 116 S.Ct. 515, 133 L.Ed.2d 424 (1995). "In particular, 'the prosecution history (or file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance.'" Teleflex, 299 F.3d at 1326 (quoting Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 452 (Fed. Cir. 1985)).[19]

Id. However, the disavowal must be unambiguous and an "applicant's choice to describe only a single embodiment does not mean that the patent clearly and unambiguously disavowed other

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> MIDs can be generated in a variety of different ways, for example, by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension.

(See '013 patent, 7:25-27) (emphasis added). Thus, the placement of "e.g." modifies the statement "MIDs can be generated in a variety of ways" to indicate that the language after it is an example. It does not modify, as Plaintiffs contend, the words "combinational tagging." The patentee's decision to place e.g. before "combination tagging approach" is intentional and indicates that they did not intend the "combinational tagging" approach to cover a multiple of different examples. Rather, based on the text, they intended for "combinational tagging" to be described as an "approach in which one MID is attached by ligation and a second MID is attached by primer extension." ('013 patent, 7:25-27).

[19] The prosecution history is viewed this way because it "ensures that claims are not construed one way in order to obtain their allowance and in a different way against accused infringers." Chimie v. PPG Industries, Inc., 402 F.3d 1371, 1384 (Fed. Cir. 2005) (citing Southwall Tech., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995)).

embodiments." Home Diagnostics, Inc. v. LifeScan, Inc., 381 F.3d 1352, 1357 (Fed. Cir. 2004). Nonetheless, "even where 'prosecution history statements do not rise to the level of unmistakable disavowal, they do inform the claim construction.'" University of Mass. v. L'Oréal S.A., 36 F.4th 1374, 1379 (Fed. Cir. 2022) (quoting Personalized Media Communications, LLC v. Apple Inc., 952 F.3d 1336, 1340 (Fed. Cir. 2020) (citations omitted)).

Here, the prosecution history, while it does not contain an explicit disavowal, nonetheless supports Defendant's proposed construction. When the '013 patent application was first filed, it did not include the term "combinational tagging" in any claim, but it was included in the specification. (See Doc. No. 105-1 at 2.) On March 12, 2020, when the applicant filed a preliminary amendment and added "combinational tagging" to the Claims, it stated that support for these claim amendments:

> can be found in the specification as originally filed. As these amendments add no new matter and are supported by the specification as originally filed.

(See id. at 1, 9.) Accordingly, these statements show that the addition of "combinational tagging" was supported by the original specification that described "combinational tagging" as a method of attaching one MID by ligation and one by primer extension. Thus, Plaintiffs attempt to expand the claim term fails because the intrinsic evidence of the Patent defined its scope.

In sum, for the reasons noted above, the intrinsic evidence supports Defendant's proposed construction because it is supported by the intrinsic evidence of the claim language, specification language and the prosecution history.[20] Because the Court's decision rests on the intrinsic

[20] In support of its argument, Plaintiffs submit the dictionary definition of "combinational" as extrinsic evidence. (See Doc. No. 104 at 20.) However, this evidence does not overcome the intrinsic evidence that supports Defendant's proposed claim construction. See David Netzer Consulting Eng'g LLC v. Shell Oil Co., 824 F.3d 989, 997 (Fed. Cir. 2016) ("extrinsic evidence may not be used to contradict claim meaning that is unambiguous in light of the intrinsic record");

evidence, it need not evaluate the extrinsic evidence. Vitronics., 90 F.3d at 1583 ("In most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic evidence.") Accordingly, "combinational tagging" is construed as an "approach in which one MID is attached by ligation and a second MID is attached by primer extension."

B. "wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence"

Claim Term	Plaintiffs 10x and Stanford University's Proposal	Defendant Parse's Proposal
"wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence"	"wherein at least 90 percent of said plurality of sample polynucleotides of interest is associated with a unique second tag sequence"	"wherein at least 90 percent of said plurality of sample polynucleotides of said cell is associated with a unique second tag sequence"

The second disputed claim term is "wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence" in Claim 13 of the '197 Patent. Claim 13 of the '197 patent reads in full:

> The method of Claim 1, wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence.

('013 Patent, cl. 13.) The parties' proposed constructions are substantially similar, but after the word "polynucleotides" Plaintiffs insert "of interest" and Defendant inserts "of said cell." (See Doc. No. 104 at 30.) Plaintiffs argue that "of interest" is the proper construction based on the plain language of the claims, specifically that "of interest" clarifies that not all polynucleotides of a cell are being sampled. (Id.) Defendant disagrees; it submits that "of said cell" is the proper

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Johns Hopkins University v. 454 Life Sciences Corp., 123 F.Supp.3d 563, 567 (D. Del 2015) ("Where the intrinsic record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper") (citing Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1308 (Fed Cir. 1999)).

construction because "of interest" injects subjective intent to the Claim and that 10x had previously agreed to Defendant's proposed construction in a prior litigation. (Id. at 34-35 (citing 10x Genomics, Inc. v. Celsee, Inc., No. 19-cv-00862-CFC-SRF (D. Del.))). Notably, Plaintiffs are not concerned with Defendant's proposed addition of "of said cell", but only argue that "of interest" clarifies that not all polynucleotides in a cell are being used in a sample.[21] (See Doc. No. 104 at 34.) As will be discussed below, Plaintiffs' concerns are unfounded, and the Court will adopt Defendant's proposed claim construction because it reflects the plain language of the patent.

As previously stated, the first step of a court's inquiry is to evaluate the plain language of the patent because "[a] claim term is generally given the 'meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.'" Littelfuse, Inc. v. Mersen USA EP Corp., 29 F.4th 1376, 1379 (Fed. Cir. 2022) (citing Phillips, 415 F.3d at 1313 (en banc)).

Here, no ordinary person skilled in the art would interpret the language in Claim 13 to mean that "all polynucleotides in a cell" are being used, because the Claim is clearly referring to "sample polynucleotides." Rather, Plaintiffs' proposed construction using the term "of interest" would inject ambiguity and subjective intent to the claim, as described below. On the other hand, Defendant's proposed construction of adding "of said cell" correctly reflects the plain language of the '197 patent. See Renishaw, 158 F.3d at 1250 ("The construction that stays true to the claim

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[21] Specifically, Plaintiffs state:

> 10x does not dispute that the sample polynucleotides come from a cell. But any argument that "sample polynucleotides" are all polynucleotides in a cell does not logically follow. The polynucleotides of interest also originate from "said cell." There is no reason that the origin of the "sample polynucleotides" necessitates a construction that "all polynucleotides" from that cell are part of the "sample."

(Doc. No. 104 at 34.)

language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.")

The Federal Circuit has rejected terms that inject subjective intent into claims. Becon Medical, Ltd. v. Bartlett, Civ. No. 18-4169, 2019 WL 3996619, at *3 (E.D. Pa. Aug. 23, 2019) (rejecting construction that would "only add confusion to the claims"); see also Really Right Stuff, LLC v. Field Optics Rsch., Inc., No. 2:20-CV-00345-DBB, 2023 WL 6377596, at *5 (D. Utah Sept. 29, 2023) (finding construction problematic since "invitation to consider subjective intent when construing the claim language invites more confusion than clarification.")

Here, "of interest" is a subjective term that a person of ordinary skill in the art would not be able to easily ascertain a proper meaning from. As Defendant properly notes:

> What does "of interest" mean? On what criteria is "of interest" supposed to be quantified? By amount? By percentage? By type? 10x's phrase opens an unclear domain of possibilities, with no guidance on what the bounds of "of interest" might be.

(Doc. No. 104 at 38.) Plaintiffs counter that "of interest" means:

> that the user of the claimed method may select the type of polynucleotides to be included in the 'sample polynucleotides' to be counted. Cells contain many types of polynucleotides, including DNA such as nuclear DNA and mitochondrial DNA (mtDNA), and RNA such as transfer RNA (tRNA), messenger RNA (mRNA), and ribosomal RNA (rRNA), that can be counted using the claimed invention. The claims of the '197 patent expressly contemplate the user may select the type of polynucleotide to be counted.

(Doc. No. 104 at 37 (internal citations omitted)). However, unlike Defendant's proposed construction that reflects the patent's claim language, Plaintiffs' proposed addition of "of interest" is a subjective term that is confusing because it is already clear from the use of the word "sample" that not all cells are being used. Thus, for these reasons, Plaintiffs' proposed claim construction will not be adopted.

Defendant's proposed claim construction, which adds "of said cell" to the term at issue is consistent with the language of the patent and is supported by intrinsic evidence. First, Defendant's proposed addition of "of said cell" is supported by the patent's claim language as a whole. As discussed previously, a court's "inquiry is not limited to an analysis of the phrase in isolation" as "a term can be defined only in a way that comports with the instrument as a whole." Id. at 792 (citing Hockerson-Halberstadt, Inc. v. Converse Inc., 183 F.3d 1369, 1374 (Fed. Cir. 1999); Markman, 517 U.S. at 389. When looking at the instrument as a whole, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." Phillips, 415 F.3d at 1314. "Because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims." Id. (citing Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1342 (Fed. Cir. 2001)).

Here, the addition of "of said cell" to Claim 13 is consistent with the patent as a whole because "of said cell" is present in Claim 1. As discussed above, Claim 13 states:

> The method of Claim 1, wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence.

('197 patent, cl. 13.) Claim 13 is a dependent claim of Claim 1. Claim 1 claims:

> A method of counting nucleic acids in a sample, the method comprising:
>
> > (a) providing a sample comprising a plurality of cells, wherein a cell of the plurality of cells comprises a plurality of sample polynucleotides;
> >
> > (b) generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides of said cell and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides comprises. . .

('197 Patent, Claim 1.) Claim 1 (b) limits the counting of sample polynucleotides to the "said cell," which based on (a) is one of the plurality of cells in the sample being analyzed. Accordingly, Claim 13's "sample polynucleotides" are the polynucleotides from each cell within the plurality

of cells in a sample. Thus, 90% of sample polynucleotides of said cell are associated with a unique second tag sequence. Accordingly, the addition of "of said cell" to Claim 13 is consistent with the language of the patent as a whole.

Finally, both parties rely on the decision of Chief Judge Connolly of the District of Delaware in 10x Genomics, Inc. v. Celsee, Inc., to support their proposed claim constructions, and predictably, reach very different conclusions on how the claim construction in Celsee affects the instant case. See generally, 10x Genomics, Inc. v. Celsee, Inc., No. 19-cv-00862-CFC-SRF. As a preliminary matter, "courts may defer to previous claim constructions" but "such decisions are made on a case by case basis, at the discretion of the court." Texas Instruments, Inc. v. Linear Technologies Corp., 182 F.Supp.2d 580, 589 (E.D. Tex. 2002) (emphasis in original); see also Malibu Boats, LLC v. Skier's Choice, Inc., No. 3:18-cv-15-JPM, 2020 WL 5026852, at *9 (E.D. Tenn. Aug. 25, 2020) (finding that the court was not bound by a previous Markman order, and "may properly be considered by the Court" but that the reasoning is "at most persuasive") (citing Powervip, Inc. v. Static Control Components, Inc., No. 1:08-CV-382, 2011 WL 2669059, at *3 (W.D. Mich. July 6, 2011)).

Celsee is a case that involved the '197 patent with 10x as plaintiff. Plaintiffs contend that in Celsee, Chief Judge Connolly construed the same term at issue here[22] to mean fewer than "all of the polynucleotides of that cell." Thus, they conclude that "10x agrees with the substance of the ruling, but respectfully submits its proposed construction [in the instant case] provides additional clarity." (Doc. No. 104 at 30.) Defendant disagrees, submitting that Plaintiffs

[22] Celsee involved claim construction of the same term at issue here; "wherein at least 90 percent of said plurality of sample polynucleotides of interest is associated with a unique second tag sequence." ('197 Patent, cl. 13.)

mischaracterized Judge Connolly's statement because ultimately the construction Defendant proposes is "exactly the same construction that Chief Judge Connolly adopted." (Id. at 38.) While this Court has already concluded that Defendant's proposed construction aligns with the plain language of the Claim itself, and the Court could end the inquiry there,[23] Chief Judge Connolly's decision in Celsee also supports Defendant's proposed construction.

> At the Markman hearing in Celsee, Chief Judge Connolly stated:
>
> The Court: . . . then it seems to me that looking at paragraph B of claim 1, the plurality of sample polynucleotides in question is a plurality of sample polynucleotides of said cell, cell being singular, and having its antecedent basis in paragraph A of claim 1.
>
> . . .
>
> Mr. Younkin: Your Honor, I think the parties' dispute here is really about whether or not the plurality of sample polynucleotides of said cell means all of the sample -- all of the polynucleotides of that cell or fewer than all of the polynucleotides of the cell.
>
> The Court: Well, it clearly means fewer than all because it's a sample. It says, the plurality of sample polynucleotide.

(Doc. No. 105-2 at 9.) Thus, despite Plaintiffs' contentions otherwise—Judge Connolly's decision supports Defendant's proposed claim construction for two reasons. First, as stated previously, Plaintiffs' central concern is that the disputed claim term not be construed as referring "to all polynucleotides of the cell." (Doc. No. 104 at 30.) Plaintiffs' concerns are unfounded, however, because both this Court and Chief Judge Connolly have found that the term does not include "all polynucleotides of the cell" because it is a sample. See page 22 supra; (Doc. No. 105-2 at 9 ("The Court: Well, it clearly means fewer than all because it's a sample. It says, the plurality of sample polynucleotide.")

[23] See Homeland, 865 F.3d at 1375 ("[t]he claim construction inquiry . . . begins and ends in all cases with the actual words of the claim.") (quoting Renishaw, 158 F.3d at 1248).

Second, in Celsee, Chief Judge Connolly construed the claim term at issue the exact way Defendant proposes to construe it here, with "of said cell" after "sample polynucleotides." (See 10x Genomics, Inc. v. Celsee, Inc., No. 19-cv-00862-CFC-SRF, Doc. No. 154 at 2.) Thus, both the plain language of the '197 patent and even a prior Markman decision on the '197 patent support Defendant's proposed construction of the claim term, which will be adopted. Accordingly, for the reasons discussed above, the claim term "wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence" will be construed as "wherein at least 90 percent of said plurality of sample polynucleotides of said cell is associated with a unique second tag sequence."

C. "random sequences"

Claim Term	**Plaintiffs 10x and Stanford University's Proposal**	**Defendant Parse's Proposal**
"random sequences"	Plain and ordinary meaning, which is "sequences having random bases"	"a sequence consisting of randomly selected bases such that the sequence is unknown in advance of the experiment"

The third disputed claim term is "random sequences" which is present in Claim 10 of the '013 patent. Claim 10 reads in full:

> The method of claim 1, wherein said second tag sequences of said plurality of oligonucleotide tags are random sequences.

('013 Patent, Claim 10.) Plaintiffs submit that "random sequences" should be construed by its plain and ordinary meaning, which is "sequences having random bases." (See Doc. No. 104 at 39.) Defendant disagrees, arguing that the term should be construed to mean "a sequence consisting of randomly selected bases such that the sequence is unknown in advance of the experiment" because it argues that a true "random" sequence requires the limitation "that the event

be unpredictable or unknown in advance." (Id. at 42.) Here, Plaintiffs' proposed claim construction will be adopted because it aligns with the language of the '013 patent.

As previously discussed, "[c]laim terms are generally accorded their ordinary meaning—that is, their meaning to a skilled artisan at the time of the invention." Intel Corp. v. Qualcomm Inc., 21 F.4th 784, 791 (Fed. Cir. 2021) (citing Phillips v. AWH Corp., 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc)); see also Markman, 517 U.S. at 389). Thus, the term must be analyzed "in a way that comports with the instrument as a whole." Intel, 21 F.4th at 792. The Federal Circuit has clarified that "[i]f we need not rely on a limitation to interpret what the patentee meant by a particular term or phrase in a claim, that limitation is 'extraneous' and cannot constrain the claim." Renishaw, 158 F.3d at 1249. Thus, when a claim term is expressed in general descriptive words, the court should not "add a narrowing modifier before an otherwise general term that stands unmodified in a claim." Id. at 1249.

Here, the term "random sequence" must be evaluated in light of Claim 10 which is a dependent claim of Claim 1. Claim 1(b)(iii) and 1(d) recites that the:

> second tag sequence distinguish[e]s said sample polynucleotide from other sample polynucleotides . . .

('013 Patent Cl. 1.) and that the sequencing of amplified polynucleotides to determine sequences corresponding to "the second tag sequence." (Id.) Then Claim 10 states that the:

> second tag sequences of said plurality of oligonucleotide tags are random sequences.

('013 Patent, Cl. 10.) Thus, based on the claim terms, it is not required that the sequences themselves be known before the ligation, only that they have randomly generated bases.

Defendant counters that the specification shows that the sequence is unknown in advance of the experiment and that the term should be construed to reflect this limitation. In evaluating a specification, "[t]he specification is the single best guide to the meaning of a disputed term." Pressure Prods. Med. Supplies, Inc. v. Greatbatch Ltd., 599 F.3d 1308, 1314–15 (Fed. Cir. 2010) (quotations omitted). And "[w]hen a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls." Martek Biosicences Corp. v. Nutrinova, Inc., 579 F.3d 1364, 1380 (Fed. Cir. 2009). However, absent a definition, the Federal Circuit is clear that courts should "avoid the danger of reading limitations from the specification into the claim." Phillips, 415 F.3d at 1322. As the Federal Circuit noted in Phillips:

> the line between construing terms and importing limitations can be discerned with reasonable certainty and predictability if the court's focus remains on understanding how a person of ordinary skill in the art would understand the claim terms. For instance, although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments. See, e.g., Nazomi Communications, Inc. v. ARM Holdings, PLC, 403 F.3d 1364, 1369 (Fed. Cir. 2005) (claims may embrace "different subject matter than is illustrated in the specific embodiments in the specification"); Liebel–Flarsheim, 358 F.3d at 906–08; Teleflex, 299 F.3d at 1327; SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121 (Fed.Cir.1985). In particular, we have expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment. Gemstar–TV Guide, 383 F.3d at 1366. That is not just because section 112 of the Patent Act requires that the claims themselves set forth the limits of the patent grant, but also because persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the embodiments.

Id.

Here, Defendant argues that the sequences must be unknown before the experiment. It bases this contention in part on the '013 patent's specification and argues that the definition of MIDs provides that "[i]dentification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present." This shows, according to Defendant, that the unique MIDs are "identified" after being associated with sample

polynucleotides. (See Doc. No. 104 at 43 (citing '013 patent, 6:55-57)). In the specification, this identification is done by sequencing. (Id.) However, Defendant's argument fails for two reasons. First, its reading of the specification is incorrect; this construction explains that one can count the number of unique MIDS (eliminating redundant copies resulting from amplification) to determine the number of polynucleotides that were present in the cell at the time of tagging, not that the sequences were unknown before this point. And second, even if the specification indicated that the sequences could be unknown before the experiment, there is no language that specifically limits the claim term to that construction. See Phillips, 415 F.3d at 1322 (holding that courts should "avoid the danger of reading limitations from the specification into the claim" and "To avoid importing limitations from the specification into the claims, it is important to keep in mind that the purposes of the specification are to teach and enable those of skill in the art to make and use the invention and to provide a best mode for doing so); See e.g., Nazomi, 403 F.3d at 1369 (claims may embrace "different subject matter than is illustrated in the specific embodiments in the specification").

However, Plaintiffs' proposed construction of "sequences having random bases" correctly reflects the claim terms based on the intrinsic evidence. As previously discussed, "[c]laim terms are generally accorded their ordinary meaning—that is, their meaning to a skilled artisan at the time of the invention." Intel, 21 F.4th 784, 791 (Fed. Cir. 2021) (citing Phillips, 415 F.3d at 1312–13).

In this case, a person skilled in the art would interpret "random sequences" as "sequences having random bases" based on the plain language of the '013 patent's claims. Based on the claim language as discussed above, the claims recite that the "second tag sequences" are "random sequences" which a person skilled in the art would interpret as meaning that the second tag

sequences are generated randomly, regardless of whether the user knows the makeup of the randomly generated sequence prior to the experiment. Accordingly, Plaintiffs' proposed construction of "sequences having random bases" will be adopted.

D. "digital count"

Claim Term	**Plaintiffs 10x and Stanford University's Proposal**	**Defendant Parse's Proposal**
"digital count"	Plain and ordinary meaning, which is "a numerical count"	Indefinite

The fourth disputed claim term is "digital count" which appears in Claim 23 of the '013 patent. Claim 23 provides:

> The method of claim 1, wherein step (e) comprises (i) determining the number of different second tags sequences associated with said sample sequence, thereby estimating the number of sample polynucleotides having said sample sequence from said single cell and/or (ii) using second tag sequences of said plurality of amplified polynucleotides to provide a digital count of said sample polynucleotides.

('013 patent, cl. 23) (emphasis added.) Plaintiffs submit that "digital count" should be construed by its plain and ordinary meaning of "a numerical count" while Defendant counters that the claim term is indefinite for two reasons: (1) "digital count" is not a known term of art, and (2) the intrinsic record provides no guidance on the terms. (Doc. No. 104 at 54.) However, for the reasons discussed below, the Court will adopt Plaintiffs' proposed claim construction.

A party seeking to prove that a claimed term is indefinite must do so by clear and convincing evidence.[24] See Sonix Tech. Co. v. Publ'ns Int'l, Ltd., 844 F.3d 1370, 1377 (Fed. Cir.

[24] As a preliminary matter, a court can make an indefiniteness determination at the claim construction phase. See Roche Diagnostics GMBJ v. Enzo Biochem, Inc., No. 04 Civ. 4046 (RJS), 2017 WL 6988709, at *4 (S.D.N.Y. Oct. 2, 2017) (citing Plus, Inc. v. Lawson Software, Inc., 700 F.3d 509, 517 (Fed. Cir. 2012) ("[I]ndefiniteness is a question of law and in effect part of claim

2017). In Nautilus, Inc. v. Biosig Instruments, Inc., the United States Supreme Court held that a patent's claim is indefinite if "read in light of the specification . . . and the prosecution history, fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." 572 U.S. 898, 901 (2014). As the Federal Circuit recognizes, the Supreme Court's standard in Nautilus strikes a balance that permits "[s]ome modicum of uncertainty" to "ensur[e] the appropriate incentives for innovation," but it also provides a "meaningful definiteness check" to prevent patent applicants from "inject[ing] ambiguity into their claims."[25] One-E-Way, Inc., v. International Trade Commission, 859 F.3d 1059, 1062-63 (Fed. Cir. 2017) (quoting Nautilus, 572 U.S. 898 at 910.)

Accordingly, a court must evaluate the "specification and the prosecution history" to see if it "provide[s] objective boundaries for those of skill in the art," but this does not require an express definition "if the meaning of the term is fairly inferable from the patent." IQASR LLC v. Wendt Corp., 825 Fed. Appx. 900, 904 (Fed. Cir. 2020) (citations omitted); see also BASF Corp. v. Johnson Matthey Inc., 875 F.3d 1360, 1366 (Fed. Cir. 2017) ("The mere observation of information [the claim term] not 'recited' does not answer the question whether a person of ordinary skill in the art would need to be given the level and measurement information to understand, with reasonable certainty.").

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construction.") Indefiniteness will be addressed here only to the extent necessary with the construction of disputed claim terms.

[25] To determine whether a particular term is indefinite, "[o]ne must bear in mind . . . that patents are 'not addressed to lawyers, or even to the public generally,' but rather to those skilled in the relevant art." Nautilus, 134 S.Ct. at 2128–29 & n.5 (quoting Carnegie Steel Co. v. Cambria Iron Co., 185 U.S. 403, 437 (1902), and citing Eibel Process Co. v. Minn. & Ont. Paper Co., 261 U.S. 45, 58, 65–66 (1923)).

The '013 patent provides a meaningful explanation of "digital count" that provides an artisan skilled in the art with an objective understanding of the term. As discussed previously, Claim 23 describes:

> using second tag sequences of said plurality of amplified polynucleotides to provide a digital count of said sample polynucleotides.

('013 patent, cl. 23) (emphasis added). Then, in the specification, the patent discloses in its discussion of MIDS that ""[i]dentification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present in the sample (or from how many original polynucleotides a manipulated polynucleotide sample was derived . . . .)."" Thus, the "identification" of the number of "MIDS" provides a "readout" to the user. The patent also elaborates that a "'Readout' means a parameter, or parameters, which are measured and/or detected that can be converted to a number or value." Id. at 10:64–66 (emphasis added). The incorporated-by-reference '897 Patent then explains what the "digital count" would be for any "readout":

> Digital measures of polynucleotides have been made, wherein measured amounts are correlated with integral numbers of countable events.

('897 Patent at 1:42–44.) Thus, a digital count is "a count" conveyed with "integral numbers." Accordingly, this definition would be clear to a skilled artisan and is not indefinite. The Court will construe the term "digital count" by giving it a plain and ordinary meaning, which is "a numerical count."

E. "adapter sequence"

Claim Term	Plaintiffs 10x and Stanford University's Proposal	Defendant Parse's Proposal
"adapter sequence"	Plain and ordinary meaning, which is "sequence of an adapter"	"sequence of an adapter, interchangeable with 'tag'"

The final dispute concerns the term "adapter sequence" which is present in two of the Giresi Patents ('207 Patent, Claim 13 and '995 Patent, Claim 18). Claim 13 of the '207 patent states:

> The method of claim 1, wherein said transposase complex comprises a second nucleic acid insert element comprising a second adapter sequence.

('207 Patent, Claim 13 (emphasis added).) And claim 18 of the '995 patent states:

> The method of claim 17, wherein said second adapter sequence comprises a second sequencing adapter sequence.

('995 Patent, Claim 18 (emphasis added).)

As noted above, Plaintiffs seek to give this language a plain and ordinary meaning, which is "sequence of an adapter." (Doc. No. 104 at 62.) Defendant agrees with Plaintiffs' construction of "sequence of an adapter," but contends that this term is interchangeable with "tag" because the Giresi/Buenrostro Patents use the term "tag" and "adapter" interchangeably. (Id. at 65.)

To resolve this dispute, a court must first turn to the patent's language to determine if the two terms "adapter" and "tag" were used interchangeably. See Bell Atlantic Network Services, Inc. v. Covad Communications Group, 262 F.3d 1258, 1271 (Fed. Cir. 2001) ("when a patentee uses a claim term throughout the entire patent specification, in a manner consistent with only a single meaning, he has defined that term "by implication."). However, two terms being related or one being an example of another does not show that those terms are interchangeable. See Apple Inc. v. Wi-LAN Inc., 25 F.4th 960, 968 (Fed. Cir. 2022). Specifically, "the use of different terms implies that they have different meanings." Baran v. Medical Device Technologies, Inc., 616 F.3d

1309, 1316 (Fed. Cir. 2010) (citing CAE Screenplates Inc. v. Heinrich GmbH, 224 F.3d 1308, 1317 (Fed. Cir. 2000)). In short, there is a "general presumption that different terms have different meanings" that can be overcome where "the evidence indicates that the patentee used the two terms interchangeably." Chi. Bd. Options Exch., Inc. v. Int'l Sec. Exch., LLC, 677 F.3d 1361, 1369 (Fed. Cir. 2012); Baran, 616 F.3d at 1316. This general purpose instructs courts in claim construction to "generally attempt to 'give meaning to all the words in [the] claims,' and avoid 'reading out' words from the claim." In re PersonalWeb Technologies LLC, 2020-1566, 2020-1568, 2020-1569, 2021 WL 3557196, at *4 (Fed. Cir. Aug. 21, 2021) (first citing Exxon Chem. Patents, Inc. v. Lubrizol Corp., 64 F.3d 1553, 1557 (Fed. Cir. 1995); then Apple Computer, Inc. v. Articulate Sys., Inc., 234 F.3d 14, 24–25 (Fed. Cir. 2000)).

Here, the patent is not using the terms "tag" and "adapter" interchangeably. Specifically, an "adapter sequence" is a "tag," but not all "tags" are "adapter sequences." For example, the patent specification defines:

> The molecular tags can comprise sequencing adapters, locked nucleic acids (LNAs), zip nucleic acids (ZNAs), RNAs, affinity reactive molecules (e.g., biotin, dig), self-complementary molecules . . . Any of the tags can further comprise fluorescence tags . . . .

('207 Patent at 16:30-36 (emphasis added).) Thus, this specification shows that a tag not only can be a "sequencing adapter," but also LNAs, ZNAs, RNAs and other things. Defendant disagrees, arguing that while this passage "states that a 'molecular tag' can have various components such as a 'sequencing adapter,' it says nothing about whether the broader terms 'tag' and 'adapter' are interchangeable." (Doc. No. 104 at 66-67.) Rather, they counter that several passages of the patent's specifications prove that "sequence adapter" means "tag." They are:

> "After the chromatin has been fragmented and tagged to produce tagged fragments of genomic DNA, at least some of the adaptor tagged fragments are sequenced to produce a plurality of sequence reads." D.I. 80, Ex. D at 14:59-62

> The method may "comprise isolating nuclei from a population of cells; and combining the isolated nuclei with the transposase and adaptors, wherein the combining results in both lysis of the nuclei to release said chromatin and production of the adaptor-tagged fragments of genomic DNA." D.I. 80, Ex. D at 14:52-56.
>
> "The chromatin is tagmented (i.e., cleaved and tagged in the same reaction) using an insertional enzyme such as Tn5 or MuA that cleaves the genomic DNA in open regions in the chromatin and adds adaptors to both ends of the fragments." D.I. 80, Ex. D at 14:27-31

(Doc. No. 104 at 66.) Defendant's argument is unpersuasive.

In Apple Inc. v. Wi-LAN Inc, discussed earlier, the Federal Circuit affirmed a claim construction rejecting the interchangeability of two claim terms when it found that the claim terms were related, but not equivalent or interchangeable. 25 F.4th 960, 969 (Fed. Cir. 2022). There, the Circuit rejected plaintiff's argument that two components of communication systems, CPE's and subscriber units, were used interchangeably in the patent at issue. The Federal Circuit held:

> These CPEs match the description of subscriber units in the background, but, unlike subscriber units, they are never used to describe components common to communication systems broadly.
>
> Thus, the written description merely reveals that a CPE is a type of subscriber unit, which Wi-LAN freely admits. The fact that a CPE is an example of a subscriber unit, however, does not show those terms are interchangeable. And there is no evidence that the patents accord CPE the same scope as subscriber unit. As such, Apple fails to show the terms are interchangeable.

Id. at 968 (citations omitted). The Federal Circuit also stated that there was no evidence proving that the patents' use of CPE limited the patent only to CPEs, especially with the absence of language limiting the patent only to CPEs. Id. at 968-69 (citing Hill-Rom Services, Inc. v. Stryker Corp., 755 F.3d 1367, 1372-73).

Here, as in Apple, the fact that a tag can be comprised of a sequence adapter does not show that these terms are interchangeable because Defendant does not point to any language that

indicates that tags can only be sequencing adapters. Rather, as discussed above, "tags can comprise sequencing adapters, locked nucleic acids (LNAs), zip nucleic acids (ZNAs), RNAs, affinity reactive molecules (e.g., biotin, dig), self-complementary molecules . . ." ('207 Patent at 16:30-36.)

Further, Defendant has not demonstrated any language that demonstrates a "clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" Hill-Rom Services, 755 F.3d at 1372 (quoting Liebel–Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 904 (Fed. Cir. 2004)). This is shown through the language of Claim 23 of the '207 Patent:

> A method for generating a sequencing library from a plurality of cells, comprising:
>
> a) lysing a plurality of cells to isolate a plurality of cell nuclei, wherein the plurality of cell nuclei comprise chromatin;
>
> b) contacting a cell nucleus of the plurality of cell nuclei with a Tn5 transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tagged fragments,
>
> wherein the Tn5 transposase complex comprises a first sequencing adapter sequence and a second sequencing adapter sequence,
>
> wherein the Tn5 transposase complex does not comprise an antibody specific to a protein that is part of chromatin,
>
> wherein a tagged fragment of the plurality of tagged fragment comprises
>
> i. a nucleotide sequence corresponding to a region of open chromatin,
>
> ii. the first sequencing adapter sequence, and
>
> iii. the second sequencing adapter sequence; and
>
> c) performing one or more nucleic acid reactions on the tagged fragment to produce a sequencing library.

('207 Patent, Cl. 23) (emphasis added).

Based on the language of Claim 23, it is clear that "sequencing adapter" and "tag" are not interchangeable because the parties previously agreed that "tagged fragments" would be construed as "polynucleotide fragments that are attached to tags." (Doc. No. 104 at 17.) Thus, if "tagged fragment" in Claim 23 were replaced with its agreed-upon construction, both "tag" and "adapter sequence" would be used in Claim 23. Under basic principles of claim construction, different terms in the same claim are not treated as interchangeable given that the patentee chose to draft those terms as different ones. See Intel, 21 F.4th at 792 (citing Antonin Scalia & Bryan A. Garner, Reading Law 176 (2012) ("Because legal drafters should not include words that have no effect, courts avoid a reading that renders some words altogether redundant.")). Further, the specification also supports this construction. In the summary, the patent states, "[i]n some cases, the molecular tags can comprise sequencing adapters." ('207 Patent at 3:49-50.) The use of the word "can" indicates that it is possible that "tags" may comprise "sequencing adapters," but that this is not the only possible composition.

For the reasons discussed above, the Court will construe the claim term "adapter sequence" as its plain and ordinary meaning, which is "sequence of an adapter."

V. CONCLUSION

In conclusion, the claim terms are construed as follows:

Claim Term	**Court's Construction**
"combinational tagging"	"approach in which one MID is attached by ligation and a second MID is attached by primer extension"
"wherein at least 90 percent of said plurality of sample polynucleotides is associated with a unique second tag sequence"	"wherein at least 90 percent of said plurality of sample polynucleotides of said cell is associated with a unique second tag sequence"
"random sequences"	Plain and ordinary meaning, which is "sequences having random bases"

"digital count"	Plain and ordinary meaning, which is "a numerical count"
"adapter sequence"	Plain and ordinary meaning, which is "sequence of an adapter"

An appropriate Order follows.